Understanding auditory verbal hallucinations

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Understanding Auditory Verbal Hallucinations: a systematic review of current evidence.

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Abstract

Objective: Auditory Verbal Hallucinations (AVHs) are core features of psychotic illness, and remain significant in predicting poor outcome and risk. There has been a wide range of approaches to understanding these experiences.

Method: A systematic literature review summarising different methods of investigation and their results; phenomenology, descriptive psychopathology, psychological, cognitive neurobiology and neuroimaging.

Results: 764 papers and texts were screened and 113 reviewed. Phenomenological studies are comparably few in number and psychopathology remains based on concepts defined in the early 20th century. Psychological models focus on voice content and emotional reaction, and suggest a continuum of AVHs from normal experience. Neuropsychological models include AVHs as misattribution of inner speech, whilst functional neuroimaging studies focus on the spontaneous activity and connectivity of auditory networks.

Conclusions: There has been a large growth in research on AVHs in recent decades dominated by neurobiological and neuroimaging studies. Future research should include focus on phenomenological aspects and AVHs change over the course of developing illness. Integration between branches of enquiry is needed and the risk is that without this, models are proposed and investigated that bear scant relevance to the symptom itself.

Key words: schizophrenia, psychosis, auditory verbal hallucination, psychopathology, neuroimaging, neurobiology.

Summations:

- Psychological models stress the importance of content and emotion
- Dimensional models propose AVHs as a continuum of normal experience
- Cognitive neurobiological models of AVHs include misattribution of inner speech, adherent memory, semantic processing errors, and abnormal connectivity

Considerations:

- Modern investigations of what constitutes the core features of AVHs are under-represented.
- Many models do not account for the rich complexity of AVH experience or how these may change over the development of a psychotic illness.
- Studies examining voice hearing in non-clinical samples have not been widely replicated and it remains unclear as to how relevant neurobiological models are in non-clinical and non-psychotic populations.

Introduction

Auditory verbal hallucinations (AVHs) occur frequently in schizophrenia and other psychotic illnesses, and are associated with significant amounts of distress, functional disability and risk (1). Although AVHs are believed to be one of the core symptoms of psychoses, AVHs can also be experienced in the context of many other disorders and syndromes, as well as in normal populations (2). AVH occur in 70% of patients with schizophrenia(3), 23% with bipolar disorder(4), 46% with borderline personality disorder (5)and have been reported in 10-20% of the general population(3). The lack of a physical test for AVHs results in a reliance on self-report of experiences, subjective presentation, clinical history and corroboration to determine when certain symptom clusters mean that a diagnosis can be made and warrant treatment. In investigating the causes of AVHs, what is and is not considered a core feature of the experience is determined by researchers with a-priori hypotheses. How we understand, conceptualise and define AVH is hence of great importance both for clinical practice, including diagnosis and the boundaries of mental illness, and for research into better treatments.

Models of AVH arise from different perspectives including descriptive psychopathology, psychology, cognitive neurobiology and neuroimaging (6-9). Each in turn examines and explains aspects of voice hearing with an evidence base and tradition of research. The conceptual framework of psychotic illness has changed in recent decades. Diagnostic categories in psychosis such as schizophrenia, schizoaffective disorder, and bipolar disorder are criticised for their lack of a point of rarity or distinction (10). There are clear moves to abandon this categorical approach in favour of a dimensional view of psychosis as a continuum from normal to abnormal experience (11, 12). However, models of AVHs are not conceived with the newer dimensional or syndrome framework of psychosis in mind (13). Historically, emphasis on psychopathology centred around the form of hallucination. AVH phenomenology was richly explored by Jaspers, Bleuler, and Kraepelin in the early twentieth century, with emphasis on form of symptoms as key defining features of categorical diagnoses (3). Within a dimensional view of psychosis, the range of diverse, subjective experiences of AVHs may indeed represent symptoms of brain dysfunction without specificity for a single disorder, or simply the extreme of normal experience. It is equally possible that the differences and complexity of AVHs in psychotic disorders represent different underlying disturbances, directly related to the pathophysiology of the disorder itself. The National Institute of Mental Health initiative to implement the Research Domain Criteria (RDoC) could serve as a stepping stone for the move away from categorical diagnoses and brings these challenges and questions increasingly into focus (14).

Aims

This review sets out to summarise current models of auditory verbal hallucinations in the context of how they have developed; descriptive psychopathology, cognitive neurobiological, psychological, dimensional and high risk models, together with their individual and collective strengths and weaknesses, as a starting point to the further integration of branches of enquiry.

Method

A Systematic review of the literature of AVHs was conducted in January 2015. Following PRISMA guidelines, a search in Medline, PubMed, EMBase and PsychInfo was conducted for neurobiological, psychological and phenomenological studies of AVH using MESH headings: auditory verbal hallucinat* OR auditory hallucinat* OR verbal hallucinat* OR (hear* voice*) OR (hallucinat* AND voice*) AND “neurobiolog* OR neuroimag* OR neurotrans* OR neurochem* OR “phenomen* OR “psychopath* OR psychol* OR cognit*. Inclusion criteria were primary studies written in English with the main focus on the definition, description or cause of auditory hallucinations. Exclusion criteria were case reports, conference abstracts, studies where AVH were assessed only as an outcome measure, papers concerning AVHs in epilepsy or other neurological disorder and intervention studies. Review papers and core textbooks were also read to ensure all relevant papers and summations of expertise were included. Given the development of methodology and growth of literature, neuroimaging research was limited to 2004-2014. See Figure 1 for study selection process.

**********Figure 1 about here**********

Results

888 papers were identified and 764 retrieved following inclusion criteria and removal of duplications. 764 articles were screened for inclusion (title and abstract) with 554 excluded. See figure 1 for details. 221 full text articles were assessed and the final review included 113 original articles. Table 1 (supplementary material) details each original paper included in the review. We give below a summation of the main findings grouped into descriptive psychopathology, psychological and phenomenological enquiry, cognitive neurobiological models and neuroimaging data. These categories demonstrate the challenge to integration of evidence and the remaining gaps in our evidence base.

<u>Descriptive Psychopathology and historical background:</u>

AVHs are classically differentiated into ‘true hallucinations’ or ‘pseudohallucinations’. By definition, true hallucinations are conceived of as indistinguishable from real perceptions except that there is no stimulus (6). For these purposes, a real

perception occurs in external objective space, has a character of objectivity, is received by the person experiencing it with an attitude of passivity, and the sensory elements which are full, fresh, and constant are unalterable by individual will. The AVHs seen in schizophrenia are conceptualised as a subset of true hallucinations and are complex in the sense they are not elementary sensations like rudimentary noises or single words. As expected they are experienced as coming from external space, the sensory qualities are clear and have all the character of objectivity. These 'voices' may be single or multiple, male or female or both and may be those of people known or recognised (9). The syntactical quality, of the 'third person' structure of AVHs in schizophrenia has diagnostic valence, but the reason this particular structure has carried such weight is less than clear. Whilst there is some change within DSM 5, these remain core features in descriptive psychopathology. In contrast, the concept of "pseudohallucinations" is derived from a formal characterization of images (6). Pseudohallucination has more recently been seen by some as a pejorative term, linked with a failure to believe experience rather than as originally intended as a capturing of other erroneous perceptions (2). Images are thought of as being figurative in nature, are subjective and occur within inner subjective space. The sensory quality of images is construed as incomplete, poorly delineated, relatively insufficient and dependent upon the will of the person experiencing the image. An understanding of this characterization of an image is helpful to underpin the formal definition of pseudohallucinations. In Kandinsky's formula pseudohallucinations (imaged type) are identical to real perceptions except for the fact that they occur in inner subjective space(9). Kräupl Taylor's formulation on the other hand defines pseudohallucinations (perceived type) as indistinguishable from true hallucinations except that insight into the abnormality of the experience is present (6, 9, 15). At the heart of the distinction is the notion that 'true' hallucinations, irrespective of any other feature, signal serious mental illness. Alongside this is the idea that 'true' hallucinations have a veridical quality to them, that is, these experiences are indistinguishable from real perceptions (16).

True hallucinations would thus, by definition have an external location and be heard in a manner indistinguishable from real sounds. External location has been used to define "true" hallucinations, and thus indicate the presence of severe mental illness. In classically defined AVHs heard in schizophrenia, Copolov showed that patients hearing more than one voice were more likely to experience these as external phenomena (17); but, in contrast, Daalman showed that internal and external AVHs were evenly distributed in psychotic and healthy voice hearers (18). Research has shown that a location of internal or external voices is not specific to certain diagnoses, and the majority of patients with schizophrenia can hear both internal and external voices. Location is also not necessarily related to distress, impairment or other clinical characteristics (19, 20). Thus whilst clinically there remains much emphasis on the form AVHs take the literature is not extensive and dates back to influences from the early 20th century.

Phenomenological enquiry:

The term “phenomenology” can refer to the detailed description of clinical features, signs and symptoms observed in pathological conditions, or alternatively to a method of analysing subjective experience that is rooted in a particular philosophical tradition. A phenomenological approach begins with the premise that the analysis of direct description can provide significant understanding into the nature of the experience itself. Todres states that in the context of a research methodology, phenomenology is characterized by a systematic investigation of subjectivity and a consideration of experience from the first-person perspective (21). The aim is to lay bare the essence of an experience and make it intelligible to others. In light of this first-person orientation, phenomenology can be viewed as the foundational science for psychopathology (3, 22), yet relatively few papers publish primary evidence on the phenomenology of AVH experience (16, 23-27). (See Table 1).

In one influential study, Nayani and David conducted a systematic study of the phenomenology of AVHs in participants with schizophrenia-spectrum diagnoses (26). They showed a pattern of increasing complexity of AVHs over time, with the addition of more voices and extended dialogues, and increased intimacy between subject and voice. Relatively few other recent studies have looked in detail at the subjective patient experience or attempted replication. Research has instead focused on specific questions, such as comparing the AVHs to thoughts, or the internal and external location, with the presumption that this specific feature was “core” or helped delineate what was AVH from other experience (17). Spatial location has been the focus of enquiry with links to underlying brain activation in one study, that shows that external location and subjective reality of AVHs is related to motor mechanisms of speech comprehension(28). Subjective vividness of AVH has been shown to be associated with sensory cortex recruitment (29).

One recent phenomenological investigation of AVH proposes four subtypes, termed ‘Constant Commanding and Commenting’, ‘Own Thought’, ‘Replay AVH’, and ‘Non-verbal AH’. McCarthy-Jones et al argue for increased emphasis on the phenomenology of experience to further understand and enrich models of voice hearing(30). There is still a need for improved empirical research on key AVH properties, in addition to that have which may be of value in explaining the relation between memory or inner speech and AVH (22). Garcia-Montes et al suggest that having an increased direct access to the experience of AVHs will assist in fine-tuning more detailed models, which are usually taken from research in basic psychology and extrapolated without further ado to the field of schizophrenia (31). The present approach could lead to a tendency to reduce symptoms or clinical phenomena to pre-made concepts which may or may not be relevant. Investigating the actual, lived experience and deriving new theories that fit the complexity of this experience is one way forward (8, 32, 33).

Psychological Models:

Voice content and emotional reaction:

In terms of content of AVHs, command hallucinations have received most attention. They do not have diagnostic power but are clinically important because of concern that the patient may act on them and hence harm may come to themselves or others. Fernyhough, building on Vygotsky's idea about the development of inner speech in children proposes inner speech begins with private speech as a form of overt, spoken speech that is not aimed at communication but rather has the format of commands, hence the ubiquity of command hallucinations in schizophrenia and other psychiatric disorders (34, 35). Inner speech models are further discussed below in cognitive neurobiological models.

The emotional reaction to, and content of, AVHs are important particularly in terms of subjective experience and risk (22). Research shows that the emotional reaction to hallucinations may trigger and contribute to the development and maintenance of AVHs (36, 37). Some report that it is not the location, frequency or complexity of AVHs that predicts "caseness", but rather the distress and anxiety caused by the subjective experience (38). In addition, hearing a dominant voice is clinically very relevant and directly linked to psychotic depression, suicide and violence (36, 39). A voice-hearer's experience with their dominant voice is proposed as a mirror of their social relationships in general, with experiences of feeling low in rank to both voices and others being associated with depression (40, 41). Cognitive behavioural therapy for AVH, and in particular for commanding voices, focuses on this power and control (42, 43).

Three studies have investigated the emotional response to voices using neuroimaging paradigms. Escarti found patients with AVHs showed increased activity in the parahippocampal gyrus and the amygdala during an auditory paradigm (44), and Sanjuan that patients with AVHs had a greater activation in the amygdala and the hippocampal gyrus than patients without hallucinations during processing of emotional words (45). This suggests that emotional control brain areas and networks are involved in voice production and that the processing of emotions may be significantly different in patient with AVHs. In the third study, Kang et al added further evidence that AVHs in schizophrenia may be related to functional disturbances of the brains emotion networks with a reduced responsiveness in the amygdala and hippocampus to negative stimuli (46).

In terms of the malevolent or benevolence of voices, few studies have looked at differences on neuroimaging paradigms, however two studies have found functional disturbances of the emotion-related networks, including reduced responsiveness in the amygdala and hippocampus associated with negative content AVHs (46, 47).

Within a dimensional understanding of psychosis, detailed below, the process by which AVH are generated would be similar along this dimension, regardless of other

symptoms or diagnostic category. The subsequent emotional reaction to anomalous auditory experience (distress, depression, anxiety) would determine illness or illness severity(48). This emotional response may in turn be explained by abnormalities in neural networks controlling emotion and emotional regulation, thus emotional regulation and affect would be the primary pathology (49). There is considerable reporting of post traumatic symptoms in psychosis, with some suggesting emotional trauma as causal pathway to psychosis, mediated by emotional instability or stress reactivity (50). However an affective response may not explain the differences between AVHs in the context of a psychotic illness as opposed to personality disorder, PTSD etc., if indeed there are differences. This is an area open for research.

AVHs as continuum of experience:

AVHs as a Dimension: Auditory verbal hallucinations can occur in otherwise healthy individuals with rates of up to 20% of the population (51). AVHs also occur in a range of non-psychotic illnesses, including in post-traumatic stress (PTSD) and borderline personality disorder (BPD) (3). To what extent the occurrence of AVH in non-clinical populations is related to our current understanding of AVH as a core symptom of psychosis is yet to be established. If AVHs are experienced by up to 20% of the normal population, it is important to ascertain whether this the same experience as AVH occurring in people with psychotic or non-psychotic illness. A recent qualitative study of AVHs in BPD showed these experiences can be longstanding and interfere with physical and emotional functioning. They also found no clear distinctions from psychotic symptoms described by patients suffering from schizophrenia (52).

One functional, magnetic resonance imaging (fMRI) study that examined voice hearers in a small non-clinical sample (n=7) showed that similar cortical areas were activated during voices as seen in schizophrenia samples, including the superior temporal sulcus, fronto-temporal language areas and the supplementary motor area (53). Another study in schizotypal personality disorder showed similar areas of activation in both psychotic and non-psychotic participants (54). Looijestjn et al investigated sound localization and demonstrated that in psychosis external AVHs were related to increased activity in the left planum temporale and right middle frontal gyrus cluster (55). The suggestion is that within a dimensional approach to AVHs, similar processes are involved in the production of AVH across diagnostic boundaries. However, Howes et al, in positron emission tomography (PET) studies showed that neurobiological distinction between clinical and non-clinical voices is possible: altered dopamine synthesis capacity does not underlie hallucinations occurring in non-clinical otherwise health groups, but is the case with patients with psychosis (56). In addition hemispheric dominance appears to be particular to AVHs in schizophrenia, and may reflect wider alterations in the schizophrenia itself(57, 58). Dierderen have also shown that reduced functional lateralisation was specific to AVHs in schizophrenia compared to healthy voice hearers (58). How closely the

experience of these voices mirrors those in psychotic disorders, and which are the differentiating features, is not well understood, and it is not clear how, if at all, they are related.

AVH in prodromal and "at high risk" groups: Whilst it is now recognised that AVHs can occur in otherwise healthy individuals, the occurrence of attenuated or infrequent AVHs have also been used to define the possible development of a psychotic illness. Recognition, enhanced treatment, and study of first episode psychosis have been the major foci in psychosis research in recent years. This task is challenging as the boundaries between what is and is not "psychosis" extends to include the earliest phase of illness, including a prodromal ultra-high risk (UHR) phase. "Transition" to psychosis is made at a point along a proposed continuum, predefined by standard criteria, yet both prediction of transition from a pre-psychotic state to psychosis, and the clinical accuracy of such a transition point is not certain (59). Lower level and infrequent AVHs are core features of UHR criteria, yet we do not really know if they are caused by the same pathology as AVHs in schizophrenia (60, 61). Structured interviews, such as the Comprehensive Assessment of At Risk Mental States (CAARMS) and Structured Interview for Psychosis Symptoms (SIPS) consider hallucinations to be defining features of the at-risk mental state (62-65). In DSM-5 the proposed attenuated psychosis syndrome, presently in the Research Domains, includes attenuated hallucinations defined as "unusual or seldom worrisome experiences, with scepticism about their reality maintained" (66). Thus the clinical significance is loosely defined along insight, vividness, frequency and distress. Yet fluctuations along these features may also be seen within chronic AVHs, and so it is important to ask; what are the features of psychotic AVHs that distinguish them from those found in healthy individuals or that define a risk state for psychosis? (67). Positive psychotic symptoms, so generically defined, may be a poor way to distinguish between normal variants in the population, prodrome of a psychotic disorder, and those who have already "made transition" to a frank psychotic disorder (68).

AVHs were not viewed as a core feature of psychosis until DSMIII and influence from Schneiderian psychopathology (19). Whilst Schneider's influence has waned in recent times, diagnostic criteria or definitions of clinical significance have yet to be redefined. Within UHR studies the presence of AVHs has mixed evidence for predicting future psychosis. Within the Dunedin longitudinal studies early presence of AVHs like experiences predicted both later psychosis and PTSD (69, 70). In the absence of the strict Schneiderian criteria, it is possible that AVHs may merely be an "epiphenomenon" within which the major difficulties in cognition, affect or other domains are more predictive of the developing illness. As neuroimaging and biological studies of AVHs have not often explored their specific presence in developing psychosis, normal or non-psychotic populations, one cannot assume that the evidence to date results from the experience of voices rather than the underlying condition (e.g. schizophrenia). It is possible that too much diagnostic and predictive

weight is placed on the presence of AVH, alternatively that the core features of AVHs that does herald clinical relevance has not been captured to date.

Cognitive Neurobiological Models

Studies retrieved and reviewed showed that four main theoretical models have arisen in recent years:

Misattribution of Inner Speech.

The theory of impaired self-monitoring in AVHs was put forward by Frith in the 1980s (71) and proposes that patients are not aware of self-generated thoughts due to impaired inner monitoring of cognitive processes. Patients thus conclude that somebody else, external to them, is the author of those thoughts. It is argued that self-monitoring deficits can explain a core group of schizophrenia symptoms characterized by a confusion of self from non-self, including AVHs, delusions of control and passivity phenomena(72). Feinberg, Allen and others further suggested AVHs could be related to an error in “corollary discharge”. This is the process by which the initiation of a thought or act, such as speech, is accompanied by an alteration in neuronal discharges that alert the individual to the fact that such a thought or act is self-generated (73, 74). With a self-generated thought or movement, accompanying signals to the sensory and motor cortex inform parts of the brain about an intended action, allowing the sensory areas to predict this possibility and code the sensory consequences as the expected consequence of this action. Allen et al. (8) showed that patients with AVHs were more likely to attribute their own speech externally than patients without AVHs. It is suggested that in schizophrenia there is a predictive coding error that accounts for the perceived externality or misattribution of internally generated speech to an external source (75, 76). There is, however, some criticism of this theory. The complexity and severity of AVHs (for example many voices speaking in the third person, making running commentary etc.) cannot be explained entirely by prediction error or inner speech model (77, 78).

Language Production

Studies have also looked at language production, speech production and perception, rather than specifically at inner speech itself in patients who experience AVHs. The left superior temporal cortex, which supports linguistic functions, has consistently been reported to activate during auditory-verbal hallucinations in schizophrenia patients (79-83). AVHs have been shown to be related to defined cortical areas linked to specific language functions. Homan et al investigated the metabolic changes in auditory hallucinations requiring a functional rather than an anatomical definition of speech production and found significant differences in Broca’s and Wernicke’s areas associated with voice hearing in patients with schizophrenia (84).

Aberrant Memory.

This model proposes that AVHs arise from aberrant memory activation and internal monitoring, and particularly fits the “voices as traumatic experiences” phenomenon. A failure of inhibition of recall and unintended memory activation results in intrusive memories arising “out of context” and with a perception of “otherness” (72, 85, 86). The model has attracted much interest, and generated speculation about the causal role of trauma in psychotic experience. Read et al suggest that the equivocation between inner memory and outer experience may be a defensive manoeuvre to avoid reliving the traumatic experience or acknowledging it as having happened. A mis-attribution of the internal memory to an external source would lead to a reduction in distress and to delusional explanations of the experience, whilst protecting against the true traumatic memory (32, 86, 87). Hippocampal hyperactivation is apparent during hallucinations, supporting this model of AVHs as traumatic intrusions (88). However the ownership, differing phenomenological experiences, complexity, location etc. are not explained by intrusive memories alone. Whilst there is evidence to suggest a higher incidence of traumatic childhood events in patients with psychosis, and in particular those with hallucinations (85), intrusive memories do not account for the more severe and complex auditory experiences; for example neutral voices commenting on actions, or benevolent voices seen as a comfort etc. that occur frequently in psychotic illnesses (36, 89).

Early Automatic Sensory Processing Errors

Patients with schizophrenia have a variety of clear cognitive deficits, centred on working memory, executive function and sensory processing. AVH may occur as the result of altered auditory processing and pre-attentive functioning, leading to a misinterpretation of auditory stimuli as voices (90, 91). When investigating schizophrenia with electroencephalogram (EEG) recordings, differences have been found in event-related potentials (ERP) when compared to normal controls (92). ERPs are the wave recording of the brain’s response to a specific sensory, cognitive, or motor event. Event-related mismatch negativity (MMN) is an ERP that is elicited by any discriminable change in stimulation irrespective of whether or not one is consciously aware of such a change (93). With the investigation of auditory differences in schizophrenia, MMN is elicited by auditory stimuli that may deviate in any number of ways from a standard, with deviations in frequency, duration, intensity and location clearly shown to elicit a different (delayed) response in subjects with AVH compared to controls (94, 95). It is proposed that the MMN is an indication of pre-attentive cognition. In schizophrenia numerous studies have shown a deficit in MMN in both the timing and amplitude (63, 92, 94). However, yet again the complexity, ownership, and rich phenomenological experience of AVHs are not readily explained by this model alone, and studies in clinical populations outside schizophrenia are largely absent(96).

Neuroimaging Studies

Cognitive neurobiological models have in part been informed by the growth of neuroimaging studies investigating AVHs, which also report primary evidence outside the four main theories detailed above. These can be grouped in to structural and functional studies:

Structural:

Evidence suggests a correlation between AVHs presence and severity of AVHs in schizophrenia and structural brain changes in grey matter volume (GMV). Decrements are found in the insula, right superior temporal and fusiform gyri, and left inferior and superior temporal gyri (including Heschl's gyrus), thalamus, left and right cerebellum, and posterior cingulate cortex (75, 97-104). Cortical thickness reduction is widespread, in frontal, parietal, occipital, and temporal lobes (105, 106). One study found associations between GMV loss and specific features of hallucination severity: symptom duration, location, frequency and intensity (107). In terms of white matter (WM), studies have found WM deficits in the frontal and temporal areas associated with AVHs, suggesting that disconnectivity in the left fronto–temporal area may contribute to the pathophysiology of AVH in schizophrenia (108, 109) with some evidence of specific focus on the arcuate fasciculus (110).

Functional and Connectivity studies

Structural studies of WM suggest deficiencies in integrity in the brain's connectivity associated with AVHs (108). Functional MRI (fMRI) studies of patients with schizophrenia and AVHs have informed models such as that of the misattribution or misidentification of inner speech (111-113). fMRI also been done when the brain is "at rest", i.e. not engaged in directed activity, and these studies demonstrate a reduced connectivity in the primary and secondary auditory cortex, and language processing areas, in patients with schizophrenia with AVHs when compared to patients without AVHs or healthy controls (53, 114-124). fMRI and PET studies have demonstrated differences in connectivity from areas known for processing and decoding speech (125-129). Spontaneous activity in auditory networks during voice hearing itself has also been shown in symptom capture studies (53, 55, 130-133). It is also suggested that patients are sensitive to hear words and may misperceive background or aberrant noise. The secondary auditory cortex is involved in object perception, i.e. deciding where a sound comes from, and thus increases in resting activity here may also result in an over-perception, attributing significance to background noise that the patient is overly disposed to hear (134-136). In addition, a reduction in "top down" modulation from higher order areas involved in speech and language processing during AVHs has been shown (137).

The difficulty in auditory and speech processing is thought to be a frontal, executive function deficit, the result of elementary neuronal dysfunction seen as a core feature of schizophrenia (138). This dysfunction may underlie not just the mechanisms of

AVHs, but cognitive distortions, thinking errors and disordered speech seen in psychosis (137, 139). Allen et al propose a combined alteration in the balance between top down modulation and bottom up processing to be key in AVHs in schizophrenia. The top down modulation is where higher brain functioning enables focus and attention on important objects and cues, and this is disordered in AVHs. This results in aberrant or spurious noise being given significance. Bottom up difficulties, result from increased resting state or spontaneous activity in the auditory cortex and lead to more “noise” for the higher brain areas to process, with subsequently more errors (8, 140).

How this “bottom up” spontaneous activity occurs is still unclear, however there is increasing studies of the brain’s resting state, and how this may be disordered in schizophrenia and AVHs. Dierks showed an increase in resting state activity in the superior and middle temporal gyrus, in a symptom capture method, which including both the secondary and primary auditory cortex during AVHs (80, 114). Other symptoms capture studies also highlight temporal to frontal language areas(54) Thus it is suggested that the auditory cortex was both “turned on”; showing increased activity in the endogenous state and “tuned in”; to orientate the perception towards an internally driven activity rather than external stimulus (134, 141, 142). Linking back to abnormalities in inner speech, some authors have investigated language networks with significant results suggesting a supra-regional network model of AVHs in schizophrenia with a selective vulnerability to AVHs the result of specific anatomical connections to posterior temporal regions (143).

Criticisms of a “top down bottom-up” include that this still does not explain the personal significance of voice content, the perception of voices as being the voice of others, or how auditory networks become activated. Building on resting state evidence, several fMRI studies in schizophrenia recently point to an elevated activity in the default mode network (DMN) (144). The DMN is a network of brain regions that are active when the individual is not focused on the outside world and the brain is at wakeful rest. It consists of the medial temporal lobe, medial prefrontal cortex and posterior cingulate cortex along with areas of the parietal cortex(145). There is a decrease in task induced deactivation (i.e. reducing activity in areas of the brain not in use during goal orientated tasks) in psychosis (146). There may be a correlation between increased connectivity within the DMN and positive symptom severity in psychosis (8). Northoff et al propose an abnormal interaction between the auditory cortex and DMN may be responsible for AVHs. A high resting state DMN induces a high resting state in the auditory cortex (134), and the subsequent abnormal interaction is experienced as an external event which is perceived as a voice(8) .

Integrating functional brain imaging findings to structural evidence, functional cerebral asymmetry has also been found. Compared to a non-hallucination schizophrenia group, the left Wernicke’s area was significantly activated by both left and right-sided voices in an auditory task (147, 148). In teasing out state vs trait aspects, Kuhn found the state of experiencing AVHs related to brain regions that

have been implicated in speech production i.e., Broca's area, whereas trait proneness to AVHs seems to be related to areas involved in auditory stimuli processing and speech perception, ie, auditory cortex (149). In terms of brain metabolism, magnetic resonance spectroscopy studies have shown some evidence of association between severity of AVHs and left temporal/Heschl gyrus metabolism (84, 150, 151).

Despite the focus clinically on external versus internal AVHs, only two brain imaging studies explored internal versus external location. Results suggested that internal location may be linked to developmental vulnerability whereas external location is specific to brain activity in the planum temporale and prefrontal regions (55), and that there may be opposite deviations in white matter volume and sulcus displacement at the temporo-parietal junction(152).

Discussion

This systematic review of studies investigating AVHs identified 113 primary papers, with approaches reflecting descriptive psychopathology, phenomenology, psychological, neurobiological and neuroimaging models. Neurobiological and neuroimaging studies have grown the most in recent years and may prove key to advancing our understanding of AVHs. However, descriptive psychopathology remains heavily influenced by the historical perspective and modern phenomenological studies are relatively few. Thus the question of whether the core features of AVHs, as elucidated by phenomenological enquiry and descriptive psychopathology, are consistent with the areas of neurobiological investigation remains open. Although AVHs are experienced by many as having a distinct 'auditory' quality (i.e. they are experienced as being heard), cognitive neurobiological models have yet to account for this phenomena, and also fail to explain the complexity of whole experience. Other models, such as Inner Speech, also struggle to account for patients' own experience of inner speech, which may be no different to healthy individuals. There also remains the question of why some patients report hearing the voice of another or multiple different voices rather than their own inner speech. Why do some patients engage in conversation or hear their own thoughts spoken aloud? Internalising parental dialogue to inner speech as development from childhood occurs, with abnormality here changing this inner speech to a voice perception, is an attractive model, explaining the command nature of come voices and linked to developing neurobiological pathways. However, whilst all the models mentioned above have some explanatory power, they are unable to explain many details and may not be able to explain all paths to AVH experience. Indeed, the current focus of investigation may be too reductionist. The attempt to define the experience using one or two pathognomonic features risks missing other perhaps more important aspects. Rather, a full and detailed understanding of the phenomenological range (experience and symptom profile) of AVHs is necessary to ensure that any model it underpins accommodates the true nature of experience.

AVHs as currently understood are not necessarily disease-related and are certainly not disease-specific. Our clinical distinctions between internal vs. external experience and hallucinations vs. pseudohallucinations may not be robust or valid (153, 154). Widely used assessment tools, such as the Psychotic Rating Scales PSYRATS (155) have defined which aspects of AVHs are to be investigated without clear evidence that these are either the aspects research should be focusing on, or those which define clinically significant experiences from “normal” voice-hearing. McCarthy-Jones et al call for AVHs subtypes to be developed to improve our understanding of the biological mechanisms; including categories of hypervigilance, inner-speech, memory and epileptic AVHs (30). This is a start to a more sophisticated understanding of experience.

Phenomenological enquiry, without presupposition, begins with taking a blank sheet approach to the exploration of symptoms and experiences without assumption. It is possible that AVHs are anchored in a very different experience to that currently rated or tested for. This is important for the development of biological models of AVH, linking into better treatments for patients. All current models fail individually to explain the full experience of AVHs; be this location, complexity, distress, loudness or other features we are not currently measuring. We are also not certain which features are the defining aspects of AVHs in psychosis, the core part of their experience that signals pathology. Detailed phenomenological enquiry, somewhat neglected since the mid-20th century in psychosis research, may be key. Within this context, given the difficulties highlighted within the UHR work, a revisiting of the phenomenology of AVHs is needed, resulting in the accurate understanding of the symptoms and experience of hearing voices in and of itself (14). In clinical practice the lack of a diagnostic test for AVH results in clinicians and researchers relying heavily on the description and history of symptoms (14, 33, 156). Thus how we define the AVHs symptom is of utmost importance, including whether sub categories and differentiation between psychotic and non-psychotic AVHs exist. It is only relatively recently, with DSMIII using Schneider’s criteria, that hallucinations became almost definitional of psychosis (19). Further exploration of AVHs in psychotic and other populations has key relevance to improving the theoretical framework within which this debate and decisions around illness and disease boundaries are made.

A dimensional continuum approach to psychosis assumes that the aetiological process underpinning the experience is the same for AVHs in normal populations, emerging mental disorder and schizophrenia with severity increasing along a continuum. Yet presently there is not sufficient evidence that this is valid. It is unclear whether the experience of AVHs differs by categorical diagnosis or stage of illness, for example first versus multiple episodes. Whether we take a categorical symptom based or dimensional approach, a thorough understanding of the experience of symptoms (that is, a true reflection of individuals’ experiences) should be the starting point of investigative models. Otherwise we run the risk of continuing to investigate

an experience whose real nature is very different to that framed by what we expect using pre-defined, possibly outdated, imported constructs.

There are limitations to this review which need to be considered. Areas of exclusion of our search included AVHs experienced in epilepsy and studies on interventions, both of which will provide further evidence and scope of understanding. Other areas of omission include a rehearsal of the more historical psychodynamic approach. However the inclusion of all aspects of AVH investigation would be beyond the scope of one review, and our aim was to highlight areas of potential further integration. In addition papers not written in English will result in differing cultural experience and explanations for voice hearing also to be excluded. Further review is needed here. However we have presented a large amount of research in summary form, and bring forward suggestion as to how these might further be investigated with a symptom specific rather than categorical diagnostic approach, in keeping with NIMH RDoC criteria (157).

We propose that future research needs to initiate with detailed understanding of the subjective experience, enabling a modern psychopathological basis to neurobiological understanding. See figure 2 for illustration. We identified a small number of researchers are beginning to look at AVHs with a truly integrated approach (33). However further studies with replication and inclusion of models reflecting the actual experience of AVHs are needed. From this increased knowledge we can then address the evidence gaps with clear implications for improved clinical interventions. In addressing key questions researchers should focus on:

1. Using a blank sheet phenomenological approach, what is the actual experience of AVHs?
2. How do AVHs change over the development of a psychotic illness? For example is complexity a measure of severity?
3. How relevant are neurobiological models of AVHs to non-clinical and non-psychotic AVHs?
4. Does a more accurately defined phenomenological experience enable newer neuroimaging and biological models to be proposed?

Studies are needed to explore the “unique” aspects, if they exist, of AVHs in schizophrenia and through the full spectrum of voice hearing populations. Information gained has the potential to inform more accurately identifiable diagnostic phenotypes, clearly observable characteristics, and further promote translational accuracy into clinical relevance.

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Figure 1: Study Selection Process

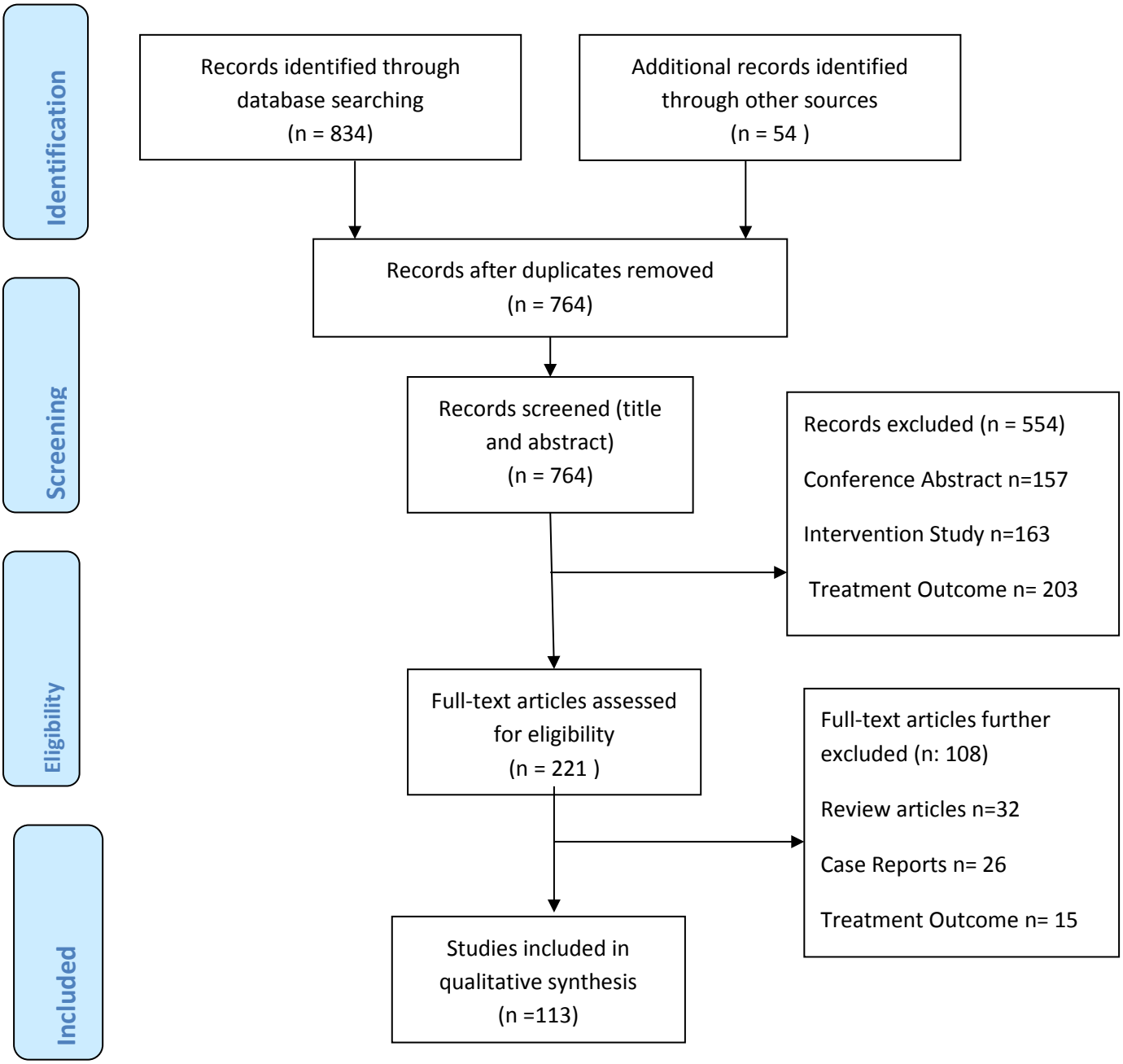
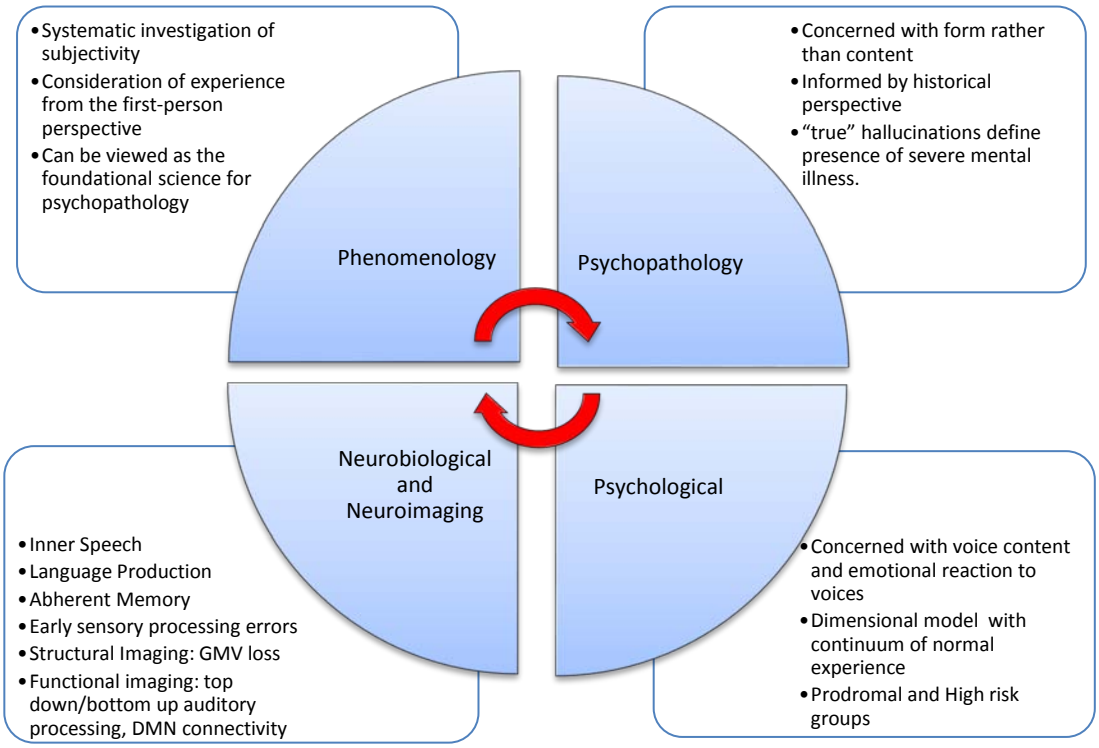


Figure 2 Current relationship between AVH models of enquiry: red arrows signal directions for increased integration



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